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14. ABSTRACT Neurofibromatosis Type 1 (NF-1) is the most common autosomal dominant genetic disorder, affecting the skin, central (CNS) and peripheral nervous systems. Children with NF-1 have an increased risk of developing significant learning disability (LD), cognitive impairment, and optic or brain stem gliomas. Cerebral magnetic resonance imaging (MRI) in NF-1 reveals regions of high signal intensity (often called "unidentified bright objects", or UBOs). The pathophysiology of UBOs is poorly understood, and it is controversial to what extent they are involved in cognitive impairment. The aims of this proposal are to characterize the underlying metabolic abnormalities in NF-1 with proton MR spectroscopic imaging (MRSI). We have developed a rapid, quantitative MR spectroscopic imaging (MRSI) protocol for the evaluation of cerebral metabolite levels in NF-1. Metabolite levels will be determined both in UBOs and other brain regions, both in order to improve understanding of the etiology of UBOs, and to understand the relationship between regional brain metabolism and LD. 60 subjects with NF1 and 60 control subjects will be evaluated with proton MRSI and detailed neuropsychological testing. Ultimately, proton MRSI may be a useful test for identifying children with NF-1 at risk of developing LD, and also help in distinguishing UBOs from other, malignant lesions which require therapeutic intervention.

15. SUBJECT TERMS
Neurofibromatosis Type 1, Magnetic Resonance Spectroscopy, Magnetic Resonance Imaging, Diagnosis

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Introduction

Neurofibromatosis Type 1 (NF-1) is the most common autosomal dominant genetic disorder, affecting the skin, central (CNS) and peripheral nervous systems. Children with NF-1 have an increased risk of developing significant learning disability (LD), cognitive impairment, and optic or brain stem gliomas. While phenotypic expression is variable, a common concern of parents of children with NF-1 is presence of learning disabilities (LD). Although the cognitive profile of NF-1 is similar to that of children with learning disabilities in the general population, with weaknesses in language, reading, and executive function commonly noted, an unusual aspect of the NF-1 profile is visuospatial impairment, which is almost always reported in NF-1 (Levine et al., 2006).

Our preliminary data used proton magnetic resonance spectroscopic imaging (MRSI), a method that allows for examination of neurochemical profiles in specific regions of the brain, reported metabolic abnormalities in the thalamus of children with NF-1 (Wang et al., 2000); however, the relationship of these findings with cognition in NF-1 was unknown at that time. Proton magnetic resonance spectroscopic imaging (MRSI) is a relatively new, non-invasive metabolic imaging technique that can provide information about the cellular composition and metabolism of brain tissue. Our preliminary proton MRSI data in NF-1 indicated highly significant perturbations in thalamic metabolism in NF-1, regardless of presence or absence of abnormalities on conventional magnetic resonance imaging (MRI) known as unidentified bright objects, or UBOs (Wang et al, 2000). UBOs themselves were metabolically more similar to normal brain tissue. These data indicated a dissociation between imaging and metabolic findings, with more widespread cerebral involvement in NF-1 depicted using MRSI than that indicated by MRI.

In this proposal, we extended these preliminary findings to confirmed that: (1) thalamic metabolism is abnormal in NF-1, (2) proton MRSI measures of thalamic metabolism correlate with neuropsychological performance, and (3) metabolic abnormalities in NF-1 are more diffuse and widespread than abnormalities visualized by MRI. The study design to test these hypotheses involved the performance of proton MRSI, MRI and neuropsychological testing in with NF-1 and age-matched control subjects. To test hypothesis (1), thalamic metabolite levels were compared between NF-1 subjects and controls. To test hypothesis (2) thalamic metabolite levels in NF-1 patients were correlated with results of a battery of neuropsychological tests, and for (3), metabolite levels in multiple regions of interest throughout the brain regions covered by MRSI were compared between NF-1 patients and controls.

Body

To understand the linkages between the neurochemical abnormalities and cognition (in addition to replicating previous findings of abnormal thalamic metabolism in children with NF-1) the current study focused on examining the relationship between MRSI metabolite ratios and cognition, specifically visuospatial processing.

Participants:

16 children with NF-1 [7 F; Overall AGE: 10.71 ± 2.73], and 35 children without NF-1 [5 F; Overall AGE: 9.89 ± 2.50] were included in the final analyses.

Judgment of Line Orientation (JLO):

This untimed visuospatial task requires the participant to decide the spatial relationship between two lines compared to a reference of a protractor-like half-circle of 11 lines. Scores are computed by tallying the number of correct responses, with a total possible score of thirty.

Boston Naming Test (BNT):

This untimed lexical access task requires naming of line-drawn objects. The 60-item test provides a measure of word retrieval efficiency as well as efficacy of semantic and phonemic cueing. Errors are broken down by type (phonemic, semantic, sequencing, circumlocution, and omission), and give information about the nature of the retrieval problem.

MRSI Data Collection:

All MR studies were performed on a Philips 1.5T Gyroscan MR scanner using the transmit-receive head coil. Prior to MRSI, a conventional brain MRI was performed consisting of sagittal T1-weighted images, and axial FLAIR and FSE T_2 scans. MR spectroscopic imaging was performed using a spin-echo sequence with two-dimensional phase-encoding and outer-volume saturation pulses for lipid suppression (2). Three 15 mm thick slices were recorded, with the middle slice placed at the level of the thalamus, and lower slices covering the brain stem and posterior fossa (common locations of UBOs in NF1) and the upper slice extending to the centrum semiovale**.** TR/TE was 1850/280 msec. A 28 by 28 circular phase-encoding scheme gave a total data acquisition time of 20 minutes (1 signal average per phase-encode step). The field-of-view was 24 cm, giving a nominal voxel size of 15.0x8.6x8.6 mm (≈ 1.1 cm^3). The echo signal was digitized with 256 data points and a spectral width of 1000 Hz. Water-suppression was accomplished with a single "CHESS" pulse with a bandwidth of 135 Hz. Extra-cranial lipid signals were attenuated by the use of 8 outer-volume saturation pulses, arranged in an octangular pattern to match the contours of the skull. T_1-weighted MR images were recorded at the same slice locations as the MRSI data set for anatomical correlation. Prior to MRSI, shimming was performed to optimize field homogeneity, and water suppression optimized. After the MRSI acquisition, a final set of

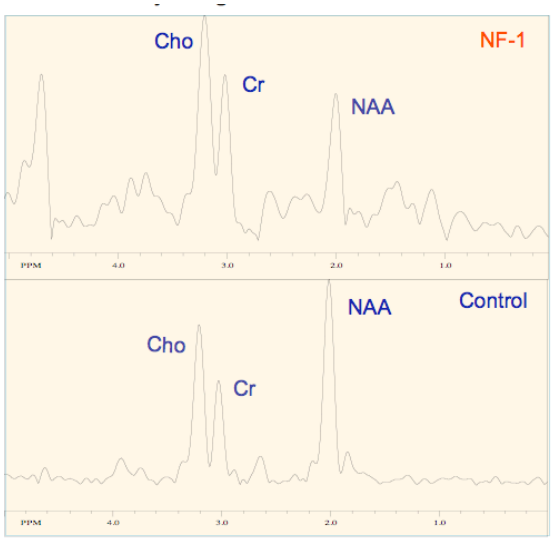

Figure 1: Right thalamic spectra showing a decreased NAA/Cho ratio in the NF1 subject

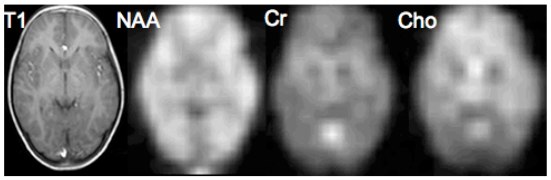

Figure 2: Localizer MRI and metabolic images in an 8 year old male NF1 subject

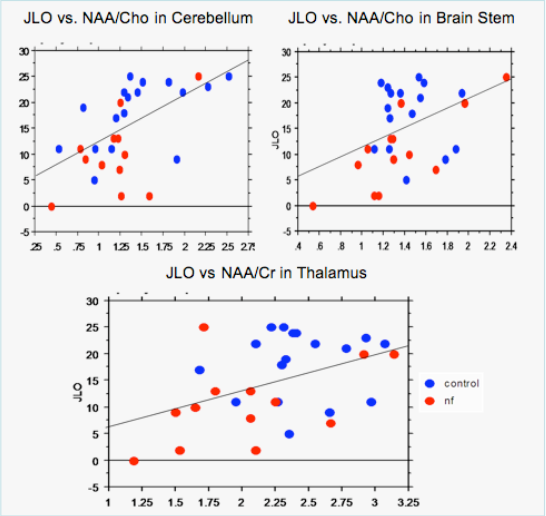

Figure 3: Regression analysis of JLO with NAA/Cho ratios in the cerebellum and brain stem, and NAA/Cr in thalamus

double gradient-echo images were also recorded at the same slice locations in order to calculate maps of the B_0 magnetic field strength.

MRSI Analyses:

Spectroscopic imaging data were reconstructed using in-house software ("csx3"). Multi-slice 2D MRSI data sets were processed via 3D Fourier transformation with cosine and Fermi filters in the spatial (phase-encoding) domains, and exponential line broadening of 3 Hz, zero-filling to 2048 data points, and a high-pass convolution filter to remove the residual water signal (50 Hz stop-band) in the time-domain. Baseline correction was performed using a cubic spline routine. After setting the chemical shift of NAA to 2.02 ppm, spectroscopic images were created by numerical integration over the following frequency ranges: Choline (3.34 to 3.14 ppm), Creatine (3.14 to 2.94 ppm), and NAA (2.22 to 1.82 ppm). Spectra from the ROIs were bilaterally evaluated by numerical integration, and ratios of metabolite peaks were calculated. The following ROIs were chosen for analysis: brain stem, cerebellum, striatum, occipital white matter, mesial occipital cortex, centrum semiovale, parietal white matter, parietal gray matter and thalamus. A student t-test was used to evaluate between group differences (NF1 vs. controls), while regression analyses performed to determine correlations between metabolite ratios and neuropsychological test scores. A P-value of less than 0.05 considered significant.

Results:

Figure 1 shows thalamic spectra from one NF1 and one control, while Figure 2 shows metabolic images from an NF1 subject at the level of the thalamus. Figure 3 shows regression analyses for JLO versus selected metabolite ratios in NF1 and controls. Lower NAA/Cr and NAA/Cho ratios in the thalamus (p=0.017 and 0.04 respectively) and in the parietal white matter (p=0.04 and 0.039 respectively) in NF1

compared to the controls. There were significant positive correlations between JLO and NAA/Cho in the brain stem, cerebellum, occipital white matter (p=0.004, 0.001, 0.019 respectively). In addition, there were significant positive correlations between JLO and NAA/Cr in the brain stem, striatum and thalamus (p=0.018, 0.03, 0.016 respectively), and a significant negative correlation between JLO and Cho/Cr ratio in the cerebellum (p=0.015). A significant positive correlation between BNT and NAA/Cr and NAA/Cho was found in the brain stem (p=0.016, 0.009 respectively), and cerebellar NAA/Cho (p=0.02).

Discussion

Reduced ratios of NAA/Cho and NAA/Cr confirm the previous observation of abnormal thalamic metabolism (1), and suggest possible thalamic neuroaxonal loss or dysfunction in NF1. Abnormal thalamic metabolism in NF1 has also been reported using positron emission tomography (3). The current finding of reduced NAA/Cr and NAA/Cho in parietal white matter also suggests more widespread white matter involvement, consistent with a previous pathological study that found myelin vacuoles in NF1.

JLO and BNT are tests of visuospatial skill and object naming, respectively, and previous studies have shown that patients with NF1 perform significantly worse on these tests compared to subjects without NF1. For this reason, these 2 tests were selected for comparison to MRSI data. JLO showed correlations with NAA/Cho and NAA/Cr in multiple brain regions, including the thalamus, striatum, brain stem and cerebellum, suggesting a link between widespread neuroaxonal dysfunction or loss in NF1 and abnormal visuospatial judgment. BNT also showed correlations with NAA/Cr and NAA/Cho ratios in brain stem and cerebellum.

Key Research Accomplishments

- Established MRSI and neuropsychological test methodology and collected data in NF1 and control subjects in the 6 to 16 year old age range.
- Statistical analysis shows significant metabolic differences between NF-1 and controls, both in the thalamus and other brain regions. These widespread metabolic changes correlated with reductions in both JLO and BNT scores, indicating an association with metabolic abnormalities and cognitive impairment.

Reportable Outcomes

M. A. Mohamed, J. R. Abel, S. L. Rimrodt, L. E. Cutting, and P. B. Barker, ISMRM 14th Annual Meeting, Seattle 2006, 2639, Proton MR Spectroscopic Imaging In Neurofibromatosis Type-1: Relationship To Neuropsychological Testing.

J.R. Abel, S.T. Rimrodt, M.A. Mohamed, L.E. Cutting and P.B. Barker, 34th Annual INS Meeting 2006, International Neuropsychological Society, Boston, MA Feb 2006, Magnetic Resonance Spectroscopic Imaging and NF-1: Correlates to Cognitive Function

Conclusions:

In conclusion, proton MRSI, in addition to MRI, may help understand the pathophysiology of brain involvement in NF1, and its relationship to cognitive impairment and learning disabilities. The data presented here suggest that MRSI may have some role in evaluating children with NF-1 who are experiencing learning disabilities and being considered for therapeutic interventions, and that there is an underlying metabolic basis (perhaps reflecting changes in brain microstructure) for cognitive impairment in children with NF-1.

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Appendices

None